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Distinct prognosis of idiopathic nonspecific interstitial pneumonia (NSIP) fulfilling criteria for undifferentiated connective tissue disease (UCTD)

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KEYWORDS
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Summary
Background: Although idiopathic nonspecific interstitial pneumonia (NSIP) was initially identified as a provisional diagnosis, the 2008 American Thoracic Society Project concluded that idiopathic NSIP is a distinct form of idiopathic interstitial pneumonia. However, an association between idiopathic NSIP and autoimmune diseases still attracts interest. In this context, a recent study proposed an intriguing concept that idiopathic NSIP is the pulmonary manifestation of undifferentiated connective tissue disease (UCTD). However, this has not been confirmed in a large number of patients with idiopathic NSIP. The present study was conducted to investigate the proportion and characteristics of patients with idiopathic NSIP who meet the criteria for UCTD.
Methods: We reviewed 47 consecutive patients with idiopathic NSIP and examined whether they met prespecified criteria for UCTD. Furthermore, we compared the clinical

Abbreviations: NSIP, nonspecific interstitial pneumonia; UIP, usual interstitial pneumonia; DIP, desquamative interstitial pneumonia; IIP, idiopathic interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; UCTD, undifferentiated connective tissue disease; CTD, connective tissue disease; PM, polymyositis; DM, dermatomyositis; SS, primary Sjögren syndrome; RA, rheumatoid arthritis; SLE, systemic lupus; SSc, systemic sclerosis; BAL, bronchoalveolar lavage.

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characteristics between patients fulfilling the UCTD criteria (UCTD-NSIP) and those not meeting them (Non-UCTD-NSIP).
Results: Of 47 patients with idiopathic NSIP, 22 (47%) met the UCTD criteria. Common symptoms associated with connective tissue diseases (CTDs) were skin change (50%) and Raynaud's phenomenon (41%) in UCTD-NSIP. UCTD-NSIP showed a female predominance and significantly higher percentages of lymphocytes with a lower CD4/CD8 ratio in bronchoalveolar lavage than Non-UCTD-NSIP. Interestingly, UCTD-NSIP had a significantly better survival than Non-UCTD-NSIP.
Conclusions: Idiopathic NSIP included subjects who fulfilled the UCTD criteria, and these subjects had different clinical characteristics with significantly better outcome than those who did not meet the criteria. These data suggest that a part, but not all, of patients with idiopathic NSIP show CTD-like features with a distinct prognosis.

Introduction

Nonspecific interstitial pneumonia was originally described as a pathologic pattern distinct from other defined interstitial pneumonias, such as usual interstitial pneumonia (UIP) and desquamative interstitial pneumonia (DIP), by Katzenstein and Fiorelli.[1] NSIP has also been shown to be associated with a variety of conditions, including connective tissue diseases (CTDs), drug reactions, and organic dust exposures.[1–6] Thus, the 2002 Joint Statement of American Thoracic Society (ATS) and European Respiratory Society (ERS) on the classification of idiopathic interstitial pneumonias (IIPs) described idiopathic NSIP as a provisional diagnosis to be further defined.[7] Interestingly, recent studies have demonstrated that NSIP is the most common histologic pattern in CTD-associated interstitial pneumonias,[2–4,8,9] and that patients with idiopathic NSIP often exhibit CTD-like features, such as autoantibodies.[10,11] The precise relationship between idiopathic NSIP and CTDs remains to be further clarified.

Kinder et al. recently proposed a very interesting hypothesis: idiopathic NSIP is the pulmonary manifestation of undifferentiated connective tissue disease (UCTD).[12] UCTD is characterized by the presence of signs and symptoms suggestive of a systemic autoimmune disease but they do not meet the criteria for defined CTDs, such as systemic lupus erythematosus (SLE), Sjögren syndrome (SS), and rheumatoid arthritis (RA).[13–17]

However, no validated criteria for the diagnosis of UCTD have been established so far. Kinder et al. proposed prespecified criteria for UCTD and investigated the proportion and characteristics of patients fulfilling their UCTD criteria in IIPs.[12] They showed that IIP patients who met the UCTD criteria had distinct features, including a female predominance, high incidence of ground-glass opacity on high-resolution computed tomography (HRCT), and NSIP pattern on surgical lung biopsy. Remarkably, the majority of patients with idiopathic NSIP (88%) met the UCTD criteria, while only a small proportion (5%) of those with idiopathic pulmonary fibrosis (IPF) fulfilled the criteria. Thus, Kinder et al. concluded that idiopathic NSIP appears to be an autoimmune disease, the pulmonary manifestation of UCTD. This hypothesis is attractive but needs to be confirmed. In particular, the study of Kinder et al. included only a small number of patients with idiopathic NSIP (17 cases). In contrast to Kinder's study, the ATS project recently supported the notion that idiopathic NSIP is a distinct clinical entity of IIPs.[18] Out of the original 306 cases of idiopathic NSIP, however, only 67 cases were identified as definite or probable idiopathic NSIP by a dynamic integrated multidisciplinary approach in the ATS project. This project also mentioned several future issues to be investigated for further confirmation of the clinical entity of idiopathic NSIP, one of which is to determine whether idiopathic NSIP is a manifestation of an autoimmune disease.

The present study was conducted to investigate the proportion of patients with idiopathic NSIP fulfilling the UCTD criteria proposed by Kinder et al. in a larger population, and to define the clinical characteristics of those patients. Furthermore, we attempted to clarify the significance of UCTD diagnosis in idiopathic NSIP.

Patients and methods

Patients and diagnostic criteria

We studied 62 consecutive patients with idiopathic NSIP who underwent open or thoracoscopic lung biopsy at our facilities from 1990 to 2009. The diagnosis of idiopathic NSIP was based on history, physical examination, HRCT, and histologic examination, in accordance with the ATS/ERS consensus classification.[7] At the initial diagnosis, none of the patients fulfilled the American College of Rheumatology (ACR) criteria for defined CTDs, such as RA, SS, systemic sclerosis (SSc), polymyositis/dermatomyositis (PM/DM), SLE, or mixed connective tissue disease (MCTD). The study protocol was approved by the Ethical Committee of the Hamamatsu University School of Medicine.

We used the criteria for UCTD proposed by Kinder et al. as defined in Table 1. Patients were diagnosed as having UCTD if they had at least one of symptoms associated with CTDs and at least one evidence of systemic inflammation listed in Table 1. Because there was the possibility of false-negative diagnosis of patients for whom fewer items listed as evidence of systemic inflammation in Table 1 were measured, the study subjects included patients with at least four items assessed as evidence of systemic inflammation.

Table 1 Diagnostic criteria for undifferentiated connective tissue disease.

Diagnostic criteria	Presence of
Symptoms associated with connective tissue disease	At least one of the following symptoms: 1. Raynaud's phenomenon 2. Arthralgias/multiple joint swelling 3. Photosensitivity 4. Unintentional weight loss 5. Morning stiffness 6. Dry mouth or dry eyes (sicca features) 7. Dysphagia 8. Recurrent unexplained fever 9. Gastroesophageal reflux 10. Skin changes (rash) 11. Oral ulceration 12. Nonandrogenic alopecia 13. Proximal muscle weakness
Evidence of systemic inflammation in the absence of infection	Positive findings for at least one of the following: 1. Antinuclear antigen 2. Rheumatoid factor 3. Anti-SCL 70 antibody 4. SS-A or SS-B antibody 5. Jo-1 antibody 6. Sedimentation rate (>two times normal), C-reactive protein

* Criteria are derived from Reference 12.

Data collection

Clinical data, including sex, age, smoking history, symptoms, treatment and outcome were obtained from patient medical records. Laboratory findings, pulmonary function tests, and bronchoalveolar lavage (BAL) data at the time of surgical lung biopsy were also recorded.

Pathological review

Lung biopsy specimens were independently reviewed by three pathologists (T.V.C., Y.N., S.I.) who were unaware of the clinical or physiological findings. In 8 cases, initial histological classification differed between the pathologist, but a consensus opinion on the overall histopathological pattern was reached. Histological classification was based on the previously published criteria for IIPs from the ATS/ERS.[7] In addition, the degree of each pathologic finding was semiquantitatively scored (absent 0, mild 1, moderate 2, and marked 3) by two pathologists (Y.N., S.I.). The pathologic findings scored included the following: alveolar inflammation, intra-alveolar macrophages, organizing pneumonia, germinal centers, fibrosis, fibroblastic foci, honeycombing, and pleural changes.

High-resolution computed tomography (HRCT)

HRCT examination of the lungs was performed on 1.0- or 1.5-mm-thick sections to evaluate radiographic abnormalities. The HRCT images were reviewed for the presence and distribution of each of the following sign: ground-glass attenuation, airspace consolidation, interlobular septal thickening, intralobular reticular opacity, thickening of bronchovascular bundles, traction bronchiectasis, honeycombing, and cysts.

Statistical analysis

For two-group comparisons involving binary data, we used the chi-square test. Comparisons involving continuous data were made using Mann–Whitney *U* test. The interobserver correlation was analyzed using Pearson's correlation coefficient. Cumulative survival probabilities were estimated using the Kaplan–Meier method. The log-rank test was used to compare survival among the groups of patients. Statistical analyses were performed using JMP Start Stastitics (SAS Institute Inc., NC, USA). A p value <0.05 was considered significant.

Results

Patient characteristics

Of the original 62 NSIP patients, six patients were excluded, because they developed PM/DM during the observation period following initial diagnosis. These six patients had fulfilled the UCTD criteria at the initial NSIP diagnosis. Among the remaining 56 patients, 47 had adequate data with $\geq$ four items as evidence of systemic inflammation among the diagnostic criteria for UCTD. Of these 47 patients, 22 (47%) met the criteria for UCTD proposed by Kinder et al.

Clinical characteristics of patients who met the criteria for UCTD (UCTD-NSIP) and those who did not meet them (Non-UCTD-NSIP) are shown in Table 2. The median age for the patients of UCTD-NSIP was similar to that for those of Non-UCTD-NSIP. The proportion of males and current smokers tended to be lower in UCTD-NSIP than in Non-UCTD-NSIP, but the differences were not statistically significant. Respiratory symptoms or signs did not significantly differ between them. In UCTD-NSIP, the most common symptom associated with CTDs was skin change (50%), followed by Raynaud's phenomenon (41%) and arthralgias/joint swelling (23%). Fourteen patients with UCTD-NSIP (64%) had $\geq$ two symptoms. In Non-UCTD-NSIP, the symptoms associated with CTDs were rarely observed.

Laboratory findings

No significant difference was found in the serum levels of lactate dehydrogenase (LDH), C-reactive protein (CRP), KL-6, or surfactant protein-D (SP-D) between UCTD-NSIP and Non-UCTD-NSIP (Table 3). There were trends for creatine phosphokinase (CPK) and sedimentation rate to be higher in

UCTD-NSIP than in Non-UCTD-NSIP, but the differences did not reach statistical significance.

Among autoantibodies, anti-nuclear antibody was most frequently found in UCTD-NSIP (68%) (Table 3). The incidence of positive anti-nuclear antibody was significantly higher in UCTD-NSIP than in Non-UCTD-NSIP ($p = 0.0262$), but the titers were not significantly different (median [range], 120 [40—320] and 120 [40—1280], respectively). The positive rates of rheumatoid factor of UCTD-NSIP were similar to those of Non-UCTD-NSIP. Anti-Jo1 antibody and PR3-ANCA were present exclusively in UCTD-NSIP.

No significant difference was found in the results of pulmonary function tests between UCTD-NSIP and Non-UCTD-NSIP, although FVC and diffusion capacity for carbon monoxide (DLco) tended to be lower in UCTD-NSIP than in Non-UCTD-NSIP (Table 3).

BAL was performed in 17 and 23 patients with UCTD-NSIP and Non-UCTD-NSIP, respectively. The percentage of BAL lymphocytes was significantly higher in UCTD-NSIP than in Non-UCTD-NSIP ($p = 0.0424$) (Table 3). In addition, the percentage of BAL macrophages and the CD4/CD8 ratio of BAL lymphocytes were significantly lower in UCTD-NSIP than in Non-UCTD-NSIP ($p = 0.0328$ and $p = 0.0145$, respectively).

Pathological findings

Cellular NSIP was histologically diagnosed in 2 of 22 patients with UCTD-NSIP and 3 of 25 those with Non-UCTD-NSIP (9.1% vs. 12.0%, respectively), and the remaining patients had fibrotic NSIP (Table 4). Regarding each pathological finding listed in Table 4, there was no significant difference in its score, although the scores of germinal center tended to be higher in UCTD-NSIP than in Non-UCTD-NSIP ($p = 0.0914$). Interobserver correlation in the score of each finding was statistically significant, but the r-values were not high (0.481—0.667).

Radiologic findings

As shown in Table 4, ground-glass attenuation and traction bronchiectasis were generally (>90%) seen in both UCTD-NSIP and Non-UCTD-NSIP. Airspace consolidation and thickening of bronchovascular bundles were more common in UCTD-NSIP than in Non-UCTD-NSIP ($p = 0.0534$ and $p = 0.0586$, respectively). Regarding distributions of abnormalities, lower zone predominance was prominent in both UCTD-NSIP and Non-UCTD-NSIP.

Table 2 Clinical characteristics of NSIP patients who fulfill the criteria for undifferentiated connective tissue disease compared with those who do not.

Characteristics	UCTD-NSIP patients[a] ($n = 22$)	Non-UCTD-NSIP patients[b] ($n = 25$)	*P* value
Age, yr	57 (24—77)[c]	58 (38—83)	n.s.
Gender, male/female	8/14	14/11	n.s.
Smoking habit, *n*			
Current/former/never	3/7/12	10/6/9	n.s.
Observation period, yr	3.8 (0.6—17.2)	4.1 (0.6—13.8)	n.s.
Symptoms and signs, *n* (%)			
Respiratory			
Cough	16 (73)	15 (60)	n.s.
Dyspnea	4 (18)	5 (20)	n.s.
Fine crackles	17 (77)	19 (76)	n.s.
Clubbing	2 (9)	2 (8)	n.s.
Systemic			
Skin change (rash)	11 (50)	1 (4)	< 0.0001
Raynaud's phenomenon	9 (41)	0 (0)	< 0.0001
Arthralgias/joint swelling	5 (23)	1 (4)	0.0477
Dysphagia	4 (18)	0 (0)	0.0258
Morning stiffness	4 (18)	0 (0)	0.0258
Proximal muscle weakness	4 (18)	0 (0)	0.0258
Sicca symptoms	3 (14)	1 (4)	n.s.
Recurrent fever	3 (14)	0 (0)	0.0287
Unintentional weight loss	1 (5)	0 (0)	n.s.
Photosensitivity	0 (0)	0 (0)	n.s.
GERD	0 (0)	1 (4)	n.s.
Oral ulceration	0 (0)	0 (0)	n.s.
Alopecia (nonandrogenic)	0 (0)	0 (0)	n.s.

UCTD, undifferentiated connective tissue disease: GERD, gastroesophageal reflux disease; n.s., not significant.
[a] NSIP patients who fulfill the criteria for UCTD.
[b] NSIP patients who do not fulfill the criteria for UCTD.
[c] Median (Range).

Treatment and outcome

Most of the patients were treated with corticosteroid or corticosteroid plus immunosuppressive agents (UCTD-NSIP 15 patients [77%]; Non-UCTD-NSIP 20 patients [80%]) (Table 5). Among the immunosuppressive agents, cyclosporine was most commonly given to the both groups. There was no significant difference in the percentage of patients receiving immunosuppressive agents or duration of the therapy between the two groups. Only one patient (5%) with UCTD-NSIP died of respiratory failure during the observation period, while eight patients (32%) with Non-UCTD-NSIP patients died. The difference was statistically significant ($p = 0.0170$). No patients with cellular NSIP died during the observation period in UCTD-NSIP or Non-UCTD-NSIP.

Table 3 Laboratory and bronchoalveolar lavage findings of NSIP patients who fulfill the criteria for undifferentiated connective tissue disease compared with those who do not.

Characteristics	UCTD-NSIP[a]	Non-UCTD-NSIP[b]	*P* value
LDH, IU/L	333 ± 149[c]	293 ± 104	n.s.
CPK, IU/L	252 ± 415	94 ± 50	n.s.
CRP, mg/dL	0.87 ± 1.00	0.60 ± 1.05	n.s.
Sedimentation rate, mm/hr	38 ± 7	22 ± 16	n.s.
KL-6, U/mL	1690 ± 1194	1792 ± 1410	n.s.
SP-D, ng/mL	261 ± 203	263 ± 132	n.s.
Anti-nuclear antibody	15/22 (68)[d]	9/25 (36)	0.0262
Rhematoid factor	3/21 (14)	4/25 (16)	n.s.
Anti-SCL 70 antibody	0/19 (0)	0/15 (0)	n.s.
Anti-SSA antibody	3/21 (14)	1/16 (6)	n.s.
Anti-SSB antibody	0/21 (0)	0/16 (0)	n.s.
Anti-Jo1 antibody	2/19 (11)	0/16 (0)	n.s.
Anti-centromere antibody	0/16 (0)	0/6 (0)	n.s.
Anti-RNP antibody	1/14 (7)	0/12 (0)	n.s.
Anti-double strand DNA antibody	1/18 (6)	0/17 (0)	n.s.
Anti-Sm antibody	0/10 (0)	0/9 (0)	n.s.
MPO-ANCA	0/12 (0)	0/13 (0)	n.s.
PR3-ANCA	1/12 (8)	0/14 (0)	n.s.
PaO_2 on room air, Torr	78 ± 13	78 ± 14	n.s.
FVC, % predicted	61 ± 15	70 ± 22	n.s.
DLco, % predicted	60 ± 17	72 ± 28	n.s.
Bronchoalveolar lavage (BAL)	$n = 17$	$n = 23$	
Total cell count, x 10^5/mL	2.62 ± 1.86	2.32 ± 2.07	n.s.
Cellular profile, %			
Macrophages	61.6 ± 30.0	84.1 ± 9.7	0.0328
Lymphocytes	28.9 ± 29.1	11.4 ± 9.8	0.0424
Neutrophils	5.6 ± 8.2	2.7 ± 2.7	n.s.
Eosinophils	3.2 ± 4.0	2.1 ± 2.8	n.s.
CD4/CD8 ratio of BAL lymphocytes	1.03 ± 1.20	2.49 ± 2.83	0.0145

UCTD, undifferentiated connective tissue disease; LDH, lactate dehydrogenase; SP-D, surfactant protein D; MPO-ANCA, myeloperoxidase antineutrophil cytoplasmic autoantibody; PR3-ANCA, proteinase 3-antineutrophil cytoplasmic antibody; VC, vital capacity; FEV1, forced vital capacity in 1 s; DLco, diffusion capacity for carbon monoxide; BAL, bronchoalveolar lavage; n.s., not significant.

[a] NSIP patients who fulfill the criteria for UCTD.

[b] NSIP patients who do not fulfill the criteria for UCTD.

[c] Mean ± SD.

[d] The number of positive results/the number tested (%).

Survival

A comparison of survival curves between the two groups is shown in Fig. 1. Patients with UCTD-NSIP had a significantly better survival rate than those with Non-UCTD-NSIP (5-year survival, 100% vs. 58%, respectively; $p = 0.0092$).

Discussion

The present study demonstrated that about half of patients with idiopathic NSIP met the criteria for UCTD proposed by Kinder et al. Comparing NSIP patients fulfilling the criteria for UCTD (UCTD-NSIP) with those who did not meet the criteria (Non-UCTD-NSIP), patients with UCTD-NSIP had a significantly higher percentage of BAL lymphocytes with a lower CD4/CD8 ratio. Interestingly, patients with UCTD-NSIP had a significantly better survival than those with Non-UCTD-NSIP. These data suggest that UCTD diagnosis based on the criteria of Kinder et al. is associated with favorable prognosis in idiopathic NSIP.

Between patients with UCTD-NSIP and those with Non—UCTD-NSIP, besides the BAL findings and prognosis, several differences were noted. A female predominance (64%) was found in UCTD-NSIP, but not in Non-UCTD-NSIP. A large proportion of patients with UCTD-NSIP presented with two or more CTD-associated symptoms and/or signs, while those with Non-UCTD-NSIP scarcely had them. On HRCT, airspace consolidation and thickening of bronchovascular bundles tended to be found more frequently in UCTD-NSIP than in Non-UCTD-NSIP (68.2% vs. 40.0%, $p = 0.0534$; 63.6% vs. 36.0, $p = 0.0586$, respectively) Taken together, these data suggest that patients fulfilling the UCTD criteria of Kinder et al. may have distinct characteristics in idiopathic NSIP.

We confirmed the study of Kinder et al. showing that idiopathic NSIP included subjects fulfilling their UCTD criteria. However, there were several discrepancies between this previous work and our study. First, the proportion of patients who met the criteria of Kinder et al. was lower in our NSIP patients than in this previous work (47% vs. 88%, respectively). Kinder et al. proposed the interesting notion that the clinical entity of idiopathic NSIP is the lung manifestation of UCTD, because most of their patients with idiopathic NSIP met the UCTD criteria.[12] However, our observations suggest that idiopathic NSIP consisted of two populations with distinct prognoses: patients fulfilling and those not fulfilling the UCTD criteria. Second, the profiles of symptoms and signs associated with CTDs were different. Kinder et al. reported that the most common symptoms and signs were GERD (65%) and arthralgias/joint swelling (64%). However, skin change and Raynaud's phenomenon were most

Table 4 Pathological and radiologic findings of NSIP patients who fulfill the criteria for undifferentiated connective tissue disease compared with those who do not.

Features	UCTD-NSIP[a]	Non-UCTD-NSIP[b]	*P* value
Pathological findings			
Cellular NSIP/Fibrotic NSIP	2/20	3/22	n.s.
Alveolar wall inflammation	2.0 ± 0.4[c]	1.9 ± 0.6	n.s.
Intra-alveolar macrophages	0.8 ± 0.4	0.8 ± 0.8	n.s.
Organizing pneumonia	0.8 ± 0.8	0.6 ± 0.7	n.s.
Germinal center	0.7 ± 1.2	0.3 ± 0.5	n.s.
Fibrosis	2.2 ± 0.6	2.2 ± 0.8	n.s.
Honey combing	0.3 ± 0.8	0.6 ± 0.3	n.s.
Pleural lesion	0.3 ± 0.9	0.3 ± 0.9	n.s.
Radiologic findings			
Ground-glass attenuation, %	95.5	92.0	n.s.
Airspace consolidation, %	68.2	40.0	0.0534
Interlobular septal thickening, %	22.7	40.0	n.s.
Intralobular reticular opacity, %	77.2	72.0	n.s.
Thickening of bronchovascular bundles, %	63.6	36.0	0.0586
Traction bronchiectasis, %	95.5	96.0	n.s.
Honeycombing, %	4.5	12.0	n.s.
Cysts, %	4.5	8.0	n.s.
Lower zone predominance, %	77.3	68.0	n.s.

UCTD, undifferentiated connective tissue disease; n.s., not significant.
[a] NSIP patients who fulfill the criteria for UCTD.
[b] NSIP patients who do not fulfill the criteria for UCTD.
[c] Scores 0-3, Mean ± SD.

frequently present in our patients with UCTD-NSIP (50% and 41%, respectively). The reason for these discrepancies is unknown. The study of Kinder et al. included only 17 patients with idiopathic NSIP, whereas we examined a relatively large number of patients (47 cases). In addition, there was a wide ethnic dissimilarity between the two studies. These differences in study population may be partly related to the discrepancies. To resolve this issue, future studies on a larger series of patients with idiopathic NSIP are necessary.

Because the disease entity of UCTD has not been fully established and there has been no validation of the criteria of Kinder et al., interpretations of our observations and those of Kinder et al. should be made with great caution. Initially, UCTD was defined as systemic autoimmune disorders with signs and symptoms that do not sufficiently fulfill the accepted classification criteria for the defined CTDs.[13] Thus, UCTD was also considered a latent or subclinical phase of the defined CTDs, developing overt CTDs later.[19,20] However, Mosca et al. demonstrated that only a small population of patients with UCTD developed the defined CTDs, in particular, early in their clinical course.[15–17] Thus, they concluded that UCTD is a clinical entity distinct from other defined CTDs. In contrast, other studies reported the relatively high prevalences (35–68%) of progression to

Table 5 Treatment and outcome of NSIP patients who fulfill the criteria for undifferentiated connective tissue disease compared with those who do not.

	UCTD-NSIP[a] (*n* = 22)	Non-UCTD-NSIP[b] (*n* = 25)	*P* value
Treatment, *n* (%)			
Corticosteroids alone	6 (36)	10 (40)	n.s.
Corticosteroids + immunosuppressive agents	9 (41)	10 (40)	n.s.
Cyclosporine	6	7	
Cyclophosphamide	2	1	
Azathioprine	1	2	
Duration of therapy, yr	3.5 (0.6–15.2)[c]	4.0 (1.2–13.6)	n.s.
Death due to respiratory failure, *n* (%)	1 (5)	8 (32)	0.0170

n.s., not significant.
[a] NSIP patients who fulfill the criteria for UCTD.
[b] NSIP patients who do not fulfill the criteria for UCTD.
[c] Mean ± SD.

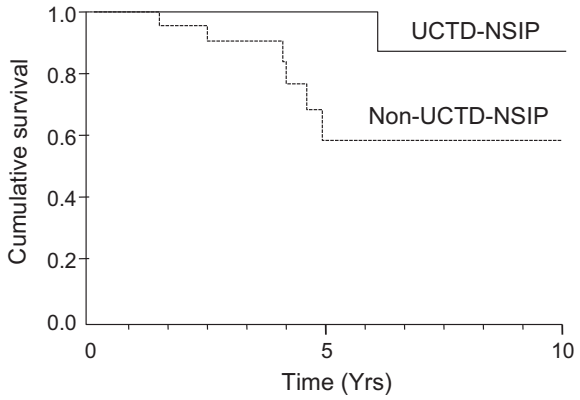

Figure 1 Survival curves of NSIP patients. Patients fulfilling the criteria of undifferentiated connective tissue disease (UCTD-NSIP) have a significantly better survival rate than those who do not fulfill (Non-UCTD-NSIP) (log-rank, $p = 0.0092$).

defined CTDs during the first and second years of follow-up in patients with UCTD.[14,19,21–23] Considering these conditions, Mosca et al. proposed criteria for UCTD as follows: (1) signs and symptoms suggestive of a CTD, but not fulfilling the criteria for any defined CTDs, (2) positive antinuclear antibodies, and (3) a disease duration of at least 3 years.[24] Importantly, the criteria of Kinder et al. used in the present study have several differences, compared with those of Mosca et al. First, the criteria of Kinder et al. does not include disease duration. As a result, patients with the defined CTDs that had not fulfilled the criteria for the defined CTDs at the initial visit, but that met the criteria of Kinder et al. for UCTD, are incorrectly diagnosed as UCTD. In those patients, anti-inflammatory and immunosuppressive treatment for NSIP often masks the later development of the overt defined CTDs. Second, although the criteria of Kinder et al. included sedimentation rate (>two times normal) and C-reactive protein as evidence of systemic inflammation (Table 1), these measurements are highly non-specific. Third, similarly, GERD listed in symptoms associated with CTDs (Table 1), which was the most common symptom in the study of Kinder et al., is not specific for CTDs. Further studies will be needed to fully define UCTD and to develop validated criteria for this disease. At present, it is, at least, true that the criteria of Kinder et al. pick out patients who have symptoms and/or signs that are suggestive of autoimmune disorders. In this context, an alternative implication of our results is that a part, but not all, of patients with idiopathic NSIP had CTD-like features but did not fulfill the criteria for the defined CTDs, and that those patients with CTD-like features showed distinct favorable prognosis. Possibly, idiopathic NSIP with CTD-like features may include true UCTD and early phases of the defined CTDs. Indeed, six (9.7%) of our 62 patents initially diagnosed with idiopathic NSIP progressed to PM/DM during the observation periods, and all the six patients had fulfilled the UCTD criteria but had not met the PM/DM criteria at the first visit.

Besides the lack of validation of the UCTD criteria we used, there are several other limitations to the present study. First, this was a retrospective study, so there were selection and recall biases. Second, although the present study included a relatively large number of patients with idiopathic NSIP, the sample size was still too small to determine the precise prevalence and clinical characteristics of those who meet the UCTD criteria.

In conclusion, we showed that idiopathic NSIP included subjects who fulfilled the UCTD criteria proposed by Kinder et al. Additionally, subjects fulfilling the UCTD criteria had different clinical characteristics with significantly better outcome than those who did not meet the criteria. These data suggest that a part of patients with idiopathic NSIP showed CTD-like features with a distinct prognosis. Future studies will be required to validate our observations.

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Conflict of interest statement

None of the authors has declared any conflict of interest related to this work.

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